L1: Entry 1 of 106 File: USPT Oct 30, 2001

DOCUMENT-IDENTIFIER: US 6309823 B1
TITLE: Arrays of nucleic acid probes for analyzing biotransformation genes and methods of using the same

BSPR:
Genetic polymorphisms of cytochromes P450 and other biotransformation enzymes result in phenotypically-distinct subpopulations that differ in their ability to perform biotransformations of particular drugs and other chemical compounds. These phenotypic distinctions have important implications for selection of drugs. For example, a drug that is safe when administered to most human may cause intolerable side-effects in an individual suffering from a defect in an enzyme required for detoxification of the drug. Alternatively, a drug that is effective in most humans may be ineffective in a particular subpopulation because of lack of a enzyme required for conversion of the drug to a metabolically active form. Further, individuals lacking a biotransformation enzyme are often susceptible to cancers from environmental chemicals due to inability to detoxify the chemicals. Eichelbaum et al., Toxicology Letters 64/65, 155-122 (1992). Accordingly, it is important to identify individuals who are deficient in a particular P450 enzyme, so that drugs known or suspected of being metabolized by the enzyme are not used, or used only with special precautions (e.g., reduced dosage, close monitoring) in such individuals. Identification of such individuals is also important so that such individuals can be subjected to regular monitoring for the onset of cancers.

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L1: Entry 3 of 106 File: USPT Oct 9, 2001

DOCUMENT-IDENTIFIER: US 6300544 B1
TITLE: Cytochrome P450 monooxygenases

BSPR:
Glucosinolates are hydrophilic, non-volatile thioglycosides found within several orders of dicotyledoneous angiosperms (Cronquist, `The Evolution and Classification of Flowering Plants, New York Botanical Garden, Bronx, 1988). The occurance of cyanogenic glucosinolates and glucosides is mutually exclusive. The greatest economic significance of glucosinolates is their presence in all members of the Brassicaceae (order of Capparales), whose many cultivars have for centuries provided mankind with a source of condiments, relishes, salad crops and vegetables as well as fodders and forage crops. More recently, rape (especially Brassica napus and Brassica campestris) has emerged as a major oil seed of commerce. About 100 different glucosinolates are known possessing the same general structure but differing in the nature of the side chain. Glucosinolates are formed from protein amino acids either directly or after a single or multiple chain extension (Underhill et al, Biochem. Soc. Symp. 38:303-326, 1973). N-hydroxy amino acids and aldoximes which have been identified as intermediates in the biosynthesis of cyanogenic glycosides also serve as efficient precursors for the biosynthesis of glucosinolates (Kindl et al, Phytochemistry 7:745-756, 1968; Matsuo et al, Phytochemistry 11:697-701, 1972; Underhill, Eur. J. Biochem. 2:61-63, 1967). Cytochrome P450.sub.I involved in cyanogenic glycoside synthesis is thus functionally very similiar to the corresponding biosynthetic enzyme in glucosinolate synthesis, and is therefore expected to be a member of the same family of P450 enzymes. Thus we have isolated a cDNA clone from Sinapis alba encoding a P450 enzyme (SEQ ID NO:17) with 54% identity to P450.sub.TYR (CYP79) and catalyzing the first step in the biosynthesis of glucosinolates, that is the formation of the aldoxime from the parent amino acid. This cDNA clone shows approximately 90% identity to an Aribidopsis EST sequence (T42902) which strongly indicates that this cytochrome P450 enzyme is highly conserved in glucosinolate containing species.

DEPR:
Reconstitution of the enzyme activity of a microsomal cytochrome P450 is accomplished by inserting the cytochrome P450 enzyme and the corresponding NADPH cytochrome P450 oxidoreductase into lipid micelles. A mixture of lipids can be used but in the case of cytochrome P450.sub.OX, dilauroylphosphatidylcholine (DLPC) provides the best enzymatic activity. The number of correctly formed complexes of cytochrome P450.sub.OX and NADPH cytochrome P450 oxidoreductase are a rate limiting factor. Excess amounts of the oxidoreductase and concentrated enzyme solutions are utilized to ensure a sufficient number of active complexes.